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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/484,537	06/07/95	QUEEN C	11823-002630

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EXAMINER	
REEVES, J	
ART UNIT	**PAPER NUMBER**
1806	15

DATE MAILED: 11/18/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/484,537	Applicant(s) Queen et al
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Jul 25, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *111-135* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *111-135* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 6, 10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. This is a continuation of application Serial No 07/634,278 which has been allowed. The claims in the above mentioned application ere directed to humanized antibodies of anti-IL-2 receptor specificity which were made through a specific humanization procedure. The claims essentially read upon antibodies which was humanized by CDR grafting and framework modifications that were determined through computer modeling and X-ray crystallography The unique property of the antibodies was that prior to applicant's work, antibodies which were humanized were not demonstrated to have comparable affinity to native antibodies. In fact CDR grafted antibodies were shown to have greatly impaired affinity. The method of humanization as taught by applicant resulted in humanized antibodies which had affinities two fold of the parental anti-IL-2 receptor antibody.

Compliance with the Sequence Requirements

2. This application contains a sequence disclosures throughout the specification that is encompassed by the definitions for nucleic acid and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, the specification fails to comply with the requirements of

37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide And/or Amino Acid Sequence Disclosures.

Specification

3. The first line of the specification needs to amended to include the status of all parent applications.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. A substitute specification is required because the case as filed is a compilation of several different applications. The specification contains four different "Background of Inventions" and several "Summaries of the Invention". Moreover, the current specification is a poor copy of the originally filed specification in the parent case. The substitute specification filed must e accompanied by a statement that it contains no new matter. Such a statement must be verified statement if made by a person not registered to practice before the Office.

6. Additionally, if there are any changes made to the specification, the drawings and descriptions of the drawings must be changed to reflect these changes. Additionally, if there are major changes to the specification, applicant is required to pint to the places in the originally disclosure which provide support of these changes.

7. Applicant should renumber the figures both in the drawings and in the Brief Description of the Drawings such that all panels are individually numbered, i.e., Figure 1 should be renumbered as Figure 1A and Figure 1B. Accordingly, the brief description of the drawings should be changed to reflect this change in the numbering scheme. Also any reference to the figures should reflect the new numbering scheme.

Claim Rejections - 35 U.S.C. § 112

8. Claims 111-135 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 111-115 are indefinite for reciting complementarity determining regions (CDRs) without reference to whether these CDRs are Kabat, Chothia or both Kabat and Chothia CDRs. The specification clearly teaches that the replaced framework amino acids fall outside both the Kabat and Chothia CDRs. The term CDRs is interpreted to mean both the Kabat and

Chothia CDRs. However, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed Cir 1993). Amending the claims to clarify this concept of CDRS would obviate this rejection.

b. Claims 114, 118, 120-123, 124-130 and 131-135, wherein they depend upon any of the proceeding are vague and indefinite for reciting affinities of "10^8 and 10^{10} M^{-1}" without a limitation that the antibodies would not be more the four fold higher affinity that the parent antibody. As written, the claims appear to recite a method of increasing antibody affinity more than four fold and for taking an low affinity antibody and producing a high affinity humanized antibody.

c. Claims 115-118 are indefinite for reciting an incomplete method claim. The method result in the production of a humanized immunoglobulin, however, only the immunoglobulin heavy chain is produced. The claims lack expression of the light chain. As antibodies are typically made up of heavy and light chains, it is not clear whether the claims intend to recite a immunoglobulin possessing only a heavy chain or an immunoglobulin possessing both a heavy and light chain.

d. Claims 111 and 115 are indefinite for reciting at least 65% identical to the donor immunoglobulin variable chain region framework. At least 65% identical reads upon donor frameworks regions that re 100% identical. These claims appear to recite completely swapping framework regions, so that none of the framework region is from the acceptor framework. These

antibodies would be CDR grafted and not reshaped antibodies, as contemplated by the specification. Inclusion of the limitation that "at least 70 amino acid residues identical to those in the acceptor human heavy chain variable region framework" would obviate this rejection.

e. Claims 111 and 115 are indefinite for reciting the abbreviation "CDRs". Full terminology should be in the first instance of the independent claims. Drop

f. Claim 115 is indefinite for reciting "humanized antibody" in line 4 as it is not clear that this phrase refers to the humanized immunoglobulin of line 2 or some other antibody. Antibody lacks proper antecedent basis. Amending the claims to recite "humanized immunoglobulin" would obviate this rejection. Drop

g. Claims 124-126 are indefinite for reciting "said amino acids" as it is not clear whether this refers to the donor amino acids or the replaced amino acids. The phrase "said amino acids" lacks proper antecedent basis in the base claim. Drop.

9. Claims 114, 118, 120-123, 124-131 and claims 132-135 that depend upon these claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. The claims are directed to embodiments which have not been enabled in the specification. For example, claims which recite the language affinity between "10^8 and 10^{10} M^{-1}", or claims that recite no affinity level have not been enabled. The specification teaches that

antibodies humanized according to applicant's methods will exhibit levels at least 60-90% of the donor immunoglobulin (see specification at page 5, lines 36-38), The examples presented in the specification are directed to various humanized antibodies two of which have been compared to affinities of the parental or donor antibodies (see Table 2, page 56). This table indicates that the humanized antibodies have either comparable affinity to the donor antibody or they had one fold less affinity. One skilled in the art would not extrapolate the affinities described in the specification to the affinities being claimed. Claims lacking an affinity encompass affinities much higher than that which was enabled in the specification. Claims reciting "10^8 and 10^{10} M^{-1}" encompass producing antibodies with affinities much higher than their parent antibody. For example, the claims encompass humanizing an antibody with an affinity of 10^5, wherein the resultant humanized antibody would have an affinity of 10^{10}. While it is well known in the art that antibodies can be screened which have very high affinities, indeed the art has shown that sheep produce a repertoire of antibodies that are very high affinity antibodies, see Groves et al, attached (Hybridoma, Vol 6(1) 71 1987), the prior art does not provide support for greatly increasing he affinity of an antibody by the claimed humanization method.

b. The state of the art at the time the invention was filed was such that one of skill in the art would have expected to lose affinity by CDR grafting (see Jones et al, Nature Vol 321 522-525 1986) or at the very best to come close to the binding affinity of the original antibody but not exceed its affinity (see Reichmann et al, Nature Vol 332, 325-327 1988). Applicant is reminded that in areas of biotechnology where unpredictability is great the burden lies with

applicant to show that the scope f his invention is within the skill of the artisan. The specification does not teach how to make humanized antibodies which exceed the affinity of parental antibody and therefore, one of ordinary skill in the art would be forced into undue experimentation in order to make the exceedingly high affinity antibodies which are within the scope of the claimed invention.

10. Claims 114, 118, 122, 123, 125-130 and claims 131-135 wherein they depend upon claims 122, 123, 125-130 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a. The claims recite a method of humanizing an immunoglobulin by replacing framework residues outside the Kabat CDRs. As evidenced by Cheetham (Protein Engineering Vol 2 (3) 170-172 1988, page 172, paragraph bridging columns 1-2, reference AM in Paper no 10) Kabat CDRs differ from Chothia CDRs and while encompass some overlapping residues, Kabat sequence CDRs may include residues that are not part of the CDRs as defined by Chothia's structural analysis and vice versa. The specification teaches replacing framework residues outside the Kabat and Chothia CDRs. See Criteria IV, pages bridging paragraph of US parent 07/310,252, in which mutations in residues that structurally are close to the border of the Kabat CDRs, but not included in the Kabat CDRs, that is residues found in the Chothia CDRs, "do not

form a part of the invention". The claims as written, now encompass replacing residues in the Chothia CDRs. This is new matter. Amending the claims to recite "Kabat and Chothia CDRs" would obviate this rejection.

11. It is noted that US application 07/290,975 (page 8, lines 3-7) provides support for the limitation "10^8 and 10^{10} M^{-1}" found in claims 114, 118, 13, 120 and 121 and claims that depend upon these. Thus these claims are entitled to the effective filing date of 2/13/89.

Claim Rejections - 35 U.S.C. § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 111 and 115 are rejected under 35 U.S.C. 102(b) as being anticipated by Reichmann et al (Nature, Vol 332, 325-327 1988), as evidenced by Cheetham (Prot Engineering Vol 2(3) 170-172, 1988, reference AM in Paper no 10).

a. The claims are directed towards a method of producing humanized antibodies wherein the variable framework region is at least 65% to the donor heavy chain variable region framework and the resulting humanized immunoglobulin. The claims are also directed towards

making humanized antibodies wherein amino acids from donor framework outside the Kabat CDR are replaced with acceptor residues and the resulting immunoglobulins.

b. Reichmann et al teach the humanization of CAMPATH-1 in which the CDRS from the donor are fitted onto a human immunoglobulin and wherein the framework regions outside the Kabat CDRs are replaced with human framework regions. Additionally, Reichmann et al teach the replacement of two residues from outside the Kabat CDRs (Ser 27 too Phe , Ser 30 to Phe) on the heavy chain variable region which dramatically increase antigen binding (see Table 1). Reichmann et al's framework re at lest 65% identical to the donor immunoglobulin. Thus the limitations of the claims have been met. As evidenced by Cheetham, serines as position 27 and30 do not fall into the Kabat CDRs, but fall into the definition of Chothia CDRs. Amending the claim to include the limitation of framework regions.

Claim Rejections - 35 U.S.C. § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 114, 118, 122-123, 126, 128, 130 and claims 132-135 that depend upon any of these claims are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Reichmann et al (Nature, Vol 332, 325-327 1988), as evidenced by Cheetham (Prot Engineering Vol 2(3) 170-172, 1988, reference AM in Paper no 10).

a. The claims are directed towards a method of producing humanized antibodies wherein the variable framework region is at least 65% to the donor heavy chain variable region framework and the resulting humanized immunoglobulin. The claims are also directed towards making humanized antibodies wherein amino acids from donor framework outside the Kabat CDR are replaced with acceptor residues and the resulting immunoglobulins.

b. Reichmann et al has been discussed above. Reichmann et al does not teach a resulting humanized antibody that has an affinity of "10^8 and 10^{10} M^{-1}" however, because that CAMPATH-1 antibody has a greatly increased binding to CAMPATH antigen, one of ordinary skill in the art would reasonably conclude that it appears the humanized CAMPATH antibody has an affinity of between "10^8 and 10^{10} M^{-1}". Therefore, it appears that Reichmann et al have produced an humanized antibody and a method of humanization that is identical to the Applicants'. Since the Patent and Trademark Office does not have the facilities for examining and comparing Applicants' antibody with the antibody of Reichmann et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed humanized antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

18. Claims 112, 116, 113, 117, 119 and claims 132-135, wherein they depend upon claim 119 are enabled by the specification and free of the prior art of record.

19. The declaration to correct the inventorship under 37 C.F.R. 1.48 (b) (paper no 4 filed 3/96) has been considered carefully adnis deemed to be sufficient. Accordingly, the anemsSchneider, Landolfi, Coelingh and Selick wil be deleted.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

21. Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

22. All Internet e-mail communications will be made of record in the application file. **PTO**

employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

23. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie C Reeves

Julie E. Reeves, Ph.D.

(703) 308-7553

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800

Paper No

15

PTO 892 is

Missing